LABELING GUIDANCE
REVISED NOVEMBER 1993
** ORIGINAL **

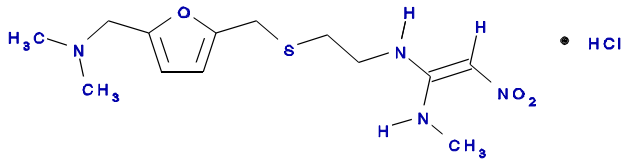
RANITIDINE TABLETS USP

DESCRIPTION

Ranitidine hydrochloride is a histamine H_2-receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino)methyl)-2-furanyl]methyl]thio]ethyl]-N' -methyl-2-nitro-1,1-ethenediamine, hydrochloride. The molecular formula is $C_{13}H_{22}N_4O_3S.HCl$, representing a molecular weight of 350.87.

Ranitidine HCl is a white to pale yellow, crystalline substance that is very soluble in water. It has a slightly bitter taste and sulfur-like odor.

The structural formula is:



Each tablet, for oral administration, contains 168 mg or 336 mg of ranitidine hydrochloride equivalent to 150 mg or 300 mg of ranitidine, respectively. In addition, each tablet contains the following inactive ingredients:

[Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance).]

CLINICAL PHARMACOLOGY

Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca^{++} in hypercalcemic states.

Ranitidine is not an anticholinergic agent.

Antisecretory Activity:

1. Effects on Acid Secretion: Ranitidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in the following table:

EFFECT OF ORAL RANITIDINE ON GASTRIC ACID SECRETION

	Time After Dose, h	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal-, nocturnal-, and betazole- stimulated secretions are most sensitive to inhibition by ranitidine, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

2. Effects on Other Gastrointestinal Secretions:

Pepsin: Oral ranitidine does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral ranitidine has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: Ranitidine has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions:

a. Gastric bacterial flora--increase in nitrate-reducing organisms, significance not known.

b. Prolactin levels--no effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

c. Other pituitary hormones--no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

d. No change in cortisol, aldosterone, androgen, or estrogen levels.

e. No antiandrogenic action.

f. No effect on count, motility, or morphology of sperm.

Pharmacokinetics:

Ranitidine hydrochloride is 50% absorbed after oral administration, compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring at 2 to 3 hours after a 150 mg dose. The elimination half-life is 2.5 to 3 hours.

Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ranitidine hydrochloride.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL/min, indicating active tubular excretion. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

In man, the N-oxide is the principal metabolite in the urine; however, this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine

half-life, distribution, clearance, and bioavailability.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Active Duodenal Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ranitidine hydrochloride as shown in the following table:

	Ranitidine HCl*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	195	69/182 (38%)†	188	31/164 (19%)
Week 4		137/187 (73%)†		76/168 (45%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$p < 0.0001$

In these studies patients treated with ranitidine reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

MEAN DAILY DOSES OF ANTACID

	Ulcer Healed	Ulcer Not Healed
Ranitidine	0.06	0.71
Placebo	0.71	1.43

Foreign studies have shown that patients heal equally well with 150 mg bid and 300 mg hs (85% versus 84%, respectively) during a usual 4-week course of therapy. If patients require extended therapy of 8 weeks, the healing rate may be higher for 150 mg bid as compared to 300 mg hs (92% versus 87%, respectively).

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ranitidine alters recurrence rates.

Maintenance Therapy in Duodenal Ulcer: Ranitidine has been found to be effective as maintenance therapy for patients following healing of acute duodenal ulcers. In two independent, double-blind, multicenter, controlled trials, the number of duodenal ulcers observed was significantly less in patients treated with ranitidine (150 mg hs) than in patients treated with placebo over a 12-month period.

DUODENAL ULCER PREVALENCE

Double-Blind, Multicenter, Placebo-Controlled Trials					
Multicenter Trial	Drug	Duodenal Ulcer Prevalence			Number of Patients
		0-4 Months	0-8 Months	0-12 Months	
USA	RAN PLC	20%* 44%	24%* 54%	35%* 59%	138 139
Foreign	RAN PLC	12%* 56%	21%* 64%	28%* 68%	174 165

% = Life-Table estimate.
* = $p < 0.05$ (ranitidine versus comparator).
RAN = ranitidine
PLC = placebo.

As with other H_2-antagonists, the factors responsible for the significant reduction in the prevalence of duodenal ulcers include prevention of recurrence of ulcers, more rapid healing of ulcers that may occur during maintenance therapy, or both.

Gastric Ulcer: In a multicenter, double-blind, controlled, US study

of endoscopically diagnosed gastric ulcers, earlier healing was seen in the patients treated with ranitidine hydrochloride as shown in the following table:

	Ranitidine HCl*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	92	16/83 (19%)	94	10/83 (12%)
Week 6		50/73 (68%)†		35/69 (51%)†

*All patients were permitted p.r.n. antacids for relief of pain.
†p = 0.009.

In this multicenter trial, significantly more patients treated with ranitidine hydrochloride became pain-free during therapy.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): Ranitidine inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison syndrome, systemic mastocytosis, and other pathological hypersecretory conditions (e.g., postoperative, "short-gut" syndrome, idiopathic). Use of ranitidine was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

Gastroesophageal Reflux Disease (GERD): In two multicenter, double-blind, placebo-controlled, 6-week trials performed in the United States and Europe, ranitidine hydrochloride 150 mg bid was more effective than placebo for the relief of heartburn and other symptoms associated with GERD. Ranitidine-treated patients consumed significantly less antacid than did placebo-treated patients.

The US trial indicated that ranitidine hydrochloride 150 mg bid significantly reduced the frequency of heartburn attacks and severity of heartburn pain within 1 to 2 weeks after starting therapy. The improvement was maintained throughout the 6-week trial period. Moreover, patient response rates demonstrated that the effect on heartburn extends through both the day and night time periods.

Erosive Esophagitis:
In two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine hydrochloride 150 mg qid was significantly more effective than placebo in healing

endoscopically-diagnosed erosive esophagitis and in relieving associated heartburn. The erosive esophagitis healing rates were as follows:

EROSIVE ESOPHAGITIS PATIENT HEALING RATES

	Healed/Evaluable	
	Placebo* n=229	Ranitidine HCl 150 mg qid * n=215
Week 4	43/198 (22%)	96/206 (47%)†
Week 8	63/176 (36%)	142/200 (71%)†
Week 12	92/159 (58%)	162/192 (84%)†

*All patients were permitted p.r.n. antacids for relief of pain.
†$p < 0.001$ versus placebo.

No additional benefit in healing of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg qid.

INDICATIONS AND USAGE

Ranitidine tablets are indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than eight weeks.

2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.

3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).

4. Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.

5. Treatment of GERD. Symptomatic relief commonly occurs within 1 or 2

weeks after starting therapy with ranitidine hydrochloride 150 mg bid.

6. Treatment of endoscopically-diagnosed erosive esophagitis. Healing of endoscopically-diagnosed erosive esophagitis occurs at 4 weeks (47%), 8 weeks (71%), and 12 weeks (84%) of therapy with ranitidine hydrochloride 150 mg qid. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

CONTRAINDICATIONS

Ranitidine is contraindicated in patients known to have hypersensitivity to the drug or any of the ingredients.

PRECAUTIONS

General:

1. Symptomatic response to ranitidine therapy does not preclude the presence of gastric malignancy.

2. Since ranitidine is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ranitidine is metabolized in the liver.

3. Rare reports suggest that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Laboratory Tests:

False-positive tests for urine protein with Multistix® may occur during ranitidine therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions:

Although ranitidine has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver.

However, there have been isolated reports of drug interactions that suggest that ranitidine may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

There was no indication of tumorigenic or carcinogenic effects in life span studies in mice and rats at dosages up to 2000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy:

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ranitidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

Ranitidine is secreted in human milk. Caution should be exercised when ranitidine hydrochloride is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in children have not been established.

Use in Elderly Patients:

Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS

The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine hydrochloride. The relationship to ranitidine therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ranitidine administration.

Central Nervous System:

Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular:

As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal:

Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic:

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg qid intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal:

Rare reports of arthralgias and myalgias.

Hematologic:

Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine:

Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine hydrochloride and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not differ from that in the general population.

Integumentary:

Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other:

Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE

There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

Studies in dogs receiving dosages of ranitidine in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer:

The current recommended adult oral dosage of ranitidine for duodenal ulcer is 150 mg twice daily. An alternative dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the

other in a particular patient population have yet to be demonstrated (see Clinical Trials: *Active Duodenal Ulcer*). Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg bid is as effective as the 150 mg dose.

Antacid should be given as needed for relief of pain (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Maintenance Therapy:

The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome):

The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ranitidine 150 mg dosages more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.

Benign Gastric Ulcer:

The current recommended adult oral dosage is 150 mg twice a day.

GERD:

The current recommended adult oral dosage is 150 mg twice a day.

Erosive Esophagitis:

The current recommended adult oral dosage is 150 mg four times a day.

Dosage Adjustment for Patients with Impaired Renal Function:

On the basis of experience with a group of subjects with severely impaired renal function treated with ranitidine, the recommended dosage in patients with a creatinine clearance less than 50 mL/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED

- Established name
- Strength of dosage form
- Packaging
- Dosage form, shape, color, imprinting, scoring
- Storage recommendations
- Date of latest revision
- "Manufactured by" statement